Remarks

Claims 198-200, 202-207, 219, 227-231, 235, 236 and 238-243 have been amended. The amendments better define the claimed invention. No new matter has been introduced by these amendments.

1. **Rejection under 35 U.S.C. § 102(b) – Peterson**

Claims 197-201, 203-211, 215-217, 219-221, 230, 234, 235 and 238-243 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,730,933 to Peterson ("Peterson"). The Examiner asserts that Peterson teaches the use of gamma radiation to sterilize a biological material such as skin, cartilage, tendon, plasma, serum, albumins, globulins, proteins, demineralized bone matrix, growth factors, *etc.*, in the presence of a stabilizer at an intensity and for a time duration sufficient to destroy substantially all microorganism contamination (citing col. 3, lines 35-65; col. 4, lines 36-51 and 59-64; and col. 6, lines 1-18). The Examiner also cites passages in Peterson in support of the alleged teaching of lyophilization of the biological material and/or the material's treatment under vacuum or in an inert atmosphere.

Applicants respectfully disagree with the Examiner's assessment of the teaching of Peterson. Peterson describes the sterilization of **extracts** of, for example, "whole blood, packed red cells, platelets, plasma (fresh or fresh frozen plasma), serum, skin, bone, cartilage, tendon, microorganisms, synthetic proteins, etc..." (col. 3, lines 42-46). There is no mention in Peterson of a biological "material" – rather, the phrase "biologically active composition" is used throughout the specification. Peterson teaches that the biological activity of the biologically active composition "is provided by a biologically active compound that is preferably a biologically active biopolymer" (col. 3, lines 40-42). It is this biologically active compound, and not the biologically active composition, that is sterilized under the conditions described by Peterson. This fact is reflected in the title, claims, Abstract and Examples of Peterson. Peterson is therefore limited to methods of sterilizing discrete components (*i.e.*, compounds) of complete systems (*i.e.*, compositions). In contrast, Applicants' independent claims 197 and 217 are directed toward methods of sterilizing the intact tissue, plasma or serum, respectively (*i.e.*, the complete systems). There is no mention in Peterson that the described method of sterilization is suitable for these complete systems. Therefore Peterson cannot anticipate claims 197, 217 and all claims dependent thereon.

As amended, Applicants' independent claim 206 is directed toward the sterilization of a protein sample that requires stabilizers not disclosed by Peterson. Because Peterson does not teach these specific stabilizers, Peterson also cannot anticipate claim 206 and all claims dependent thereon.

2. Rejection under 35 U.S.C. § 103(a) – Peterson

Claims 202 and 223-226 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson. With respect to claim 202, the Examiner asserts that although Peterson fails to expressly teach sterilization of a combination of hard and soft tissue, Peterson does disclose the sterilization of both soft and hard tissues. With respect to claim 223, the Examiner asserts that it would have been obvious to a skilled artisan to increase the total dose of radiation as necessary to achieve adequate sterilization based on Peterson's teaching of applying a dose of about 1 to about 3 mRad. With respect to claim 224-226, the Examiner asserts that it would have been obvious to optimize the concentration of the stabilizer based on Peterson's teaching of using a stabilizer in a concentration of about 0.01 to about 10 weight percent.

Applicants respectfully disagree with the Examiner's application of the teachings of Peterson to Applicants' claimed invention. As stated in section 1 above, Peterson does not teach the sterilization of tissue itself, but only biologically active compounds isolated or extracted from the tissue. Given that Peterson acknowledges that it "is often difficult to sterilize biologically active compounds since the chemical, physical or physiological properties of active compounds are often significantly altered by variations in the compounds' surrounding environment," it would likely require undue experimentation on behalf of a skilled artisan to modify the teaching of Peterson to render it suitable for sterilizing intact systems, such as tissue, or complex biological media such as serum or plasma. For at least this reason, claims 202 and 223-226 are both novel and unobvious in light of Peterson.

Regarding claim 223, the total dose recited by Applicants is at least 45 kGy, which is substantially greater than the upper limit of 30 kGy taught by Peterson. While the Examiner contends that Peterson also discloses that the conditions of sterilization are those that result in a substantial destruction of the microorganism contamination, Applicants note that Peterson also requires that at least 10 percent of the biological activity of the irradiated sample must be preserved. Thus, a skilled artisan would not be motivated by a reading to Peterson to exceed the disclosed upper limit of 30 kGy due to the perceived risk of causing a reduction of greater than 90% of the biological activity of the irradiated sample.

Regarding claims 224-226, since Peterson is directed toward the sterilization of compounds rather than whole systems, so at least as these claims are dependent from independent claims 197 and 217, optimization of the amount of stabilizer would likely require undue experimentation given the clear difference in the nature of the samples to be irradiated (the proteinaceous component in Peterson vs. Applicants' intact tissue, plasma or serum). Regarding claim 206, the recited stabilizers are different than those disclosed by Peterson, so there would have been no expectation of success on the part of a skilled

artisan to use the disclosed range of amounts of free-radical scavengers taught by Peterson. For at least the reasons stated above, Applicants request that the rejection of claims 202 and 223-226 as unpatentable over Peterson be withdrawn.

3. Rejection under 35 U.S.C. § 103(a) – Peterson in view of Horowitz

Claims 212-214, 228, 233, 236 and 237 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson in view of U.S. Patent 5,981,163 to Horowitz *et al.* ("Horowitz"). With respect to claims 212-214, the Examiner asserts that Peterson teaches the sterilization of proteins such as globulins, hormones, growth factors, and blood products but not the sterilization of clotting factors or immunoglobulins. According to the Examiner, Horowitz teaches the sterilization of clotting factors and immunoglobulins using a combination of radiation and a stabilizer. With respect to claim 228, the Examiner asserts that Peterson fails to teach mannitol as a stabilizer but that Horowitz does disclose the use of an irradiation stabilizer selected from polyhydric alcohols (such as mannitol), rutin, glutathione and others. With regard to claim 233, the Examiner asserts that Peterson fails to teach adding a sensitizer to the sample prior to irradiation but that Horowitz does disclose such an additive. With regard to claims 236 and 237, the Examiner asserts that Peterson teaches lyophilization of the sample but not that the removed solvent is an organic solvent. According to the Examiner, Horowitz teaches a sterilization step that involves treatment with an organic solvent.

Applicants respectfully disagree with the Examiner's rejection of claims 212-214, 228, 233, 236 and 237. Regarding claims 212-214 and 228, Applicants have indicated in section 1 above that amended claim 206, upon which claims 212-214 are dependent, utilizes stabilizers not taught by Peterson. Horowitz does not remedy this deficiency. Horowitz discloses that mannitol is a type I quencher and must be used in combination with a type II quencher to achieve satisfactory inactivation of contaminating viruses while still maintaining the integrity of the irradiated biological sample. No type II quenchers, as taught by Horowitz, are recited in amended claim 206.

While claim 233 does recite a sensitizer and claims 236 and 237 are directed toward a residual solvent that is an organic solvent, Horowitz cannot remedy the previously discussed deficiencies present in Peterson that allow Applicants to clearly distinguish independent claims 197, 206 and 217, from which claims 233, 236 and 237 depend. For at least the reasons stated above, Applicants request that the rejection of claims 212-214, 228, 233, 236 and 237 as being unpatentable over Peterson in view of Horowitz be withdrawn.

4. **Rejection under 35 U.S.C. § 103(a) – Peterson in view of Zabal**

Claim 218 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson in view of the abstract entitled "Contamination of fetal bovine serum with bovine viral diarrhea virus" by Zabal *et al.* ("Zabal"). The Examiner asserts that Peterson does not teach the sterilization of FBS but that Zabal does disclose that it was known in the art at the time of Applicants' invention to employ gamma radiation for this purpose.

As discussed in section 1 above, claim 217, from which claim 218 depends, is clearly distinguishable over Peterson. Zabal cannot correct the deficiencies present in Peterson that prevent Peterson from rendering claims 217 or 218 anticipated or obvious. Applicants therefore request that this rejection be withdrawn.

5. **Rejection under 35 U.S.C. § 103(a) – Peterson in view of Chanderkar**

Claim 222 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson in view of the article entitled "The involvement of aromatic amino acids in biological activity of bovine fibrinogen as assessed by gamma-irradiation" by Chanderkar *et al.* ("Chanderkar"). The Examiner asserts that Peterson does not teach a rate at which to apply the gamma radiation but that Chanderkar does disclose sterilization of fibrinogen in the presence of potassium iodide at a gamma radiation dose rate of 7.5 kGy/hr.

As discussed in section 1 above, claims 197, 206 and 217, from which claim 222 alternatively depends, are clearly distinguishable over Peterson. Chanderkar cannot correct the deficiencies present in Peterson that prevent Peterson from rendering claims 196, 206, 217 or 222 anticipated or obvious. Applicants therefore request that this rejection be withdrawn.

6. **Rejection under 35 U.S.C. § 103(a) – Peterson in view of Freistedt**

Claim 227 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson in view of the abstract of DD 280466 to Freistedt *et al.* ("Freistedt"). The Examiner asserts that Peterson does not teach DMSO as a stabilizer but that Freistedt does disclose a method of tissue sterilization wherein a stabilizer such as DMSO is added to the tissue prior to irradiation.

Freistedt cannot remedy the deficiencies present in Peterson that prevent Peterson from rendering claims 197, 206 and 216 from which claim 227 alternatively depends, as anticipated or obvious. Applicants therefore request that this rejection of claim 227 be withdrawn.

7. **Rejection under 35 U.S.C. § 103(a) – Peterson in view of Okrongly**

Claim 229 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson in view of U.S. Patent 5,283,034 to Okrongly *et al.* ("Okrongly"). The Examiner asserts that Peterson does not teach DMSO (the Examiner likely intended to say "polyols" rather than "DMSO" based on the remainder of the assertion) but that Okrongly does disclose polyols such as mannitol and trehalose.

As discussed section 1 above, claims 197 and 216, from which claim 229 alternatively depends, are clearly distinguishable over Peterson for reasons unrelated to the specific stabilizers recited. While claim 206, from which claim 229 also alternatively depends, does recite trehalose as a stabilizer, claim 206 does not also include a surface-stabilizing agent as required by Okrongly. According to Okrongly, "the compositions of the invention contain at least one surface stabilizing agent which is a relatively high molecular weight moiety adherent to the coated surface, such as HSA, BSA, collagen or ovalbumin, or is a glycoprotein..." (col. 4, lines 10-16). A skilled artisan would not be motivated, after a reading of Okrongly, to choose an oxygen radical scavenger such as trehalose in the absence of the also-required surface stabilizing agent. As such, claim 229 is neither anticipated nor obvious in view of the combination of Peterson with Okrongly. Applicants request that this rejection be withdrawn.

8. **Rejection under 35 U.S.C. § 103(a) – Peterson in view of Freistedt and Horowitz**

Claims 231 and 232 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Peterson in view of Freistedt and Horowitz. The Examiner asserts that Peterson does not teach the combined use of DMSO and mannitol but that Freistedt teaches the combination of DMSO and a polyol and that Horowitz teaches a stabilizer/scavenger that can be mannitol, glycerol and others.

As discussed section 1 above, claims 197 and 216, from which claims 231 and 232 indirectly and alternatively depend, are clearly distinguishable over Peterson for reasons unrelated to the specific stabilizers recited. While claim 206, from which claims 231 and 232 also indirectly and alternatively depend, does contemplate DMSO, mannitol and trehalose as a stabilizer, the Examiner is improperly using hindsight in citing as obvious a specific combination out of many possibilities in which there is no motivation to combine. Applicants request that this rejection of claims 231 and 232 be withdrawn.

9. **Conclusion**

Upon consideration of the foregoing, it will be recognized that Applicants have fully and appropriately responded to all of the Examiner's rejections. Accordingly, all claims are believed to be in

proper form in all respects and a favorable action on the merits is respectfully requested. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is invited to contact Applicants' undersigned representative to expedite prosecution.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP

Dated: **March 2, 2005**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: 202-739-3000

Gregory T. Lowen
Registration No. 46,882